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Meeting abstract

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Study of the polymorphism Mad1 G558A in a Mexican population and its relationship with the generation of aneuploidy

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Background

Chromosomal segregation in eukaryotic cells is controlled by a group of proteins that constitute the mitotic spindle checkpoint (MSC). Any alteration in this checkpoint causes chromosomal instability, mainly aneuploidy. MAD1 is one of the MSC proteins, which has structural and regulatory functions that influence the cell cycle progress. MAD1 regulates positively MAD2, attracting it to the active kinetochore, and promoting its interaction with CDC20. This complex inhibits progression of the cell cycle towards anaphase until all chromosomes have the adequate alignment. Recently, it was reported a polymorphism at codon 558 of Mad1 gene that replaces a G for an A, promoting the change from arginine to histidine (H). The allelic frequencies in cancer cell lines were 67% for A558 and 33% for G558. Data demonstrated that the H/H phenotype affects binding between MAD1 and MAD2, disturbing the activation of the MSC. This polymorphism was only observed in cancer cells, but not in cells from healthy donors. Even though, preliminary studies in our laboratory have detected the homozygous polymorphic variant in healthy donors. The aim of the present work was to determine the frequency of the G558A polymorphism in Mad1 gene of a Mexican population, as well as its influence on the MSC activation.

Materials and methods

Whole blood samples were obtained from 140 Mexican healthy donors. DNA isolation was performed by the standard protocols (phenol-chloroform-isoamilic alcohol) and precipitated with ice-cold ethanol. Genotyping of Mad1 polymorphism (G558A) was performed by PCR and restriction-enzyme digestion. After digestion, wild type genotype generates five fragments (12, 42, 43, 50 and 94 bp), while the polymorphic variant leads the amplification of four fragments (12, 43, 50 and 136 bp). In order to investigate activation of the MSC in the polymorphic individuals, cells from 27 donors were cultured and exposed to nocodazole (0.2 μg/ml) for 2 and 6 h. Cells were fixed and stained to analyze the mitotic index.

Results

Of the 140 studied donors, 34 had GG genotype, 74 GA and 34 AA, with a genotypic frequency of 24.3, 51.4 and 24.3 respectively, and a frequency of 50% for both alleles. Treatment with nocodazole induced a higher mitotic index in lymphocytes with GG genotype, followed by the heterozygous (GA) and finally by the homozygous AA.

Conclusion

This study demonstrates that the polymorphic variant A558 of Mad1 gene is very frequent in healthy Mexican individuals, and therefore is not a result of the malignant transformation process as had been proposed. The Mad1 polymorphic variant has an influence in the cellular response to the treatment with agents that alter the chromosomal segregation. The fact that cells of the individuals of the AA variant do not stop in metaphase after treatment with nocodazole makes cells more sensitive to present errors in the chromosomal segregation, which may eventually result in the generation of aneuploid cells.